

What is claimed is:

1. A conjugate comprising:

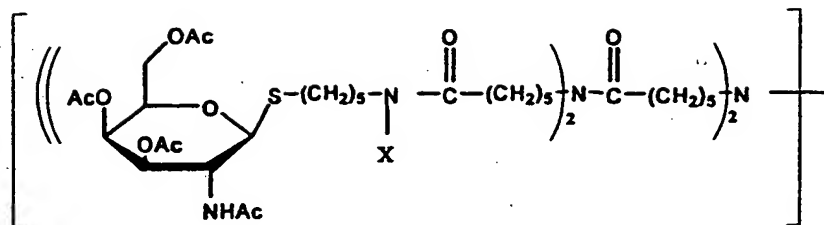
a modified annexin, wherein the modification provides an accessible sulfhydryl group; and

a hexose moiety recognized by a mammalian liver receptor, wherein the hexose moiety is conjugated to the annexin.

2. The conjugate of claim 1, wherein the hexose moiety comprises a cluster containing at least three hexose residues connected in a branched configuration, and wherein the cluster is conjugated via a single point of attachment to the annexin.

3. The conjugate of claim 2, wherein the hexose residues are independently selected from the group consisting of galactose, mannose, mannose 6-phosphate, N-acetylglucosamine, pentamannosyl phosphate, glucose, N-galactosamine, N-acetylgalactosamine, thioglycosides of galactose, D-galactosides and glucosides.

4. The conjugate of claim 3, wherein the hexose residue is N-acetylgalactosamine, and wherein the cluster comprises:



wherein X is H or CH₃.

5. The conjugate of claim 1 or 4, wherein the
 5 annexin is annexin V.

6. The conjugate of claim 5, wherein the amino acid
 at position 316 of the annexin is mutated to serine.

10 7. The conjugate of claim 5, wherein the
 modification of the annexin comprises an amino acid
 extension at the N-terminus, the amino acid extension
 comprising the accessible sulfhydryl group.

15 8. The conjugate of claim 7, wherein the extension
 comprises at least about ten amino acids.

9. The conjugate of claim 7, wherein the extension
 comprises at least about six amino acids.

20 10. The conjugate of claim 1 wherein the accessible
 sulfhydryl group is provided by cysteine.

11. The conjugate of claim 7, wherein the accessible sulfhydryl group is provided by cysteine.

12. The conjugate of claim 1 or 11, wherein the conjugate further comprises a diagnostic radionuclide complexed directly to the modified annexin.

13. The conjugate of claim 12, wherein the radionuclide is selected from the group consisting of F-18, Cu-64, Ga-67, Ga-68, Re-186, Re-188, I-123, I-125, Cu-67, Tc-99m, Tc-94, Ru-95 and In-111.

14. The conjugate of claim 13, wherein the radionuclide is technetium-99m.

15. A conjugate comprising:

a modified annexin, wherein the modification provides an accessible sulfhydryl group;

a hexose moiety recognized by a mammalian liver receptor; and

a N_xS_y chelating compound, wherein the hexose moiety is conjugated to the modified annexin directly or via the chelating compound and the chelating compound is conjugated to the modified annexin directly or via the hexose moiety.

16. The conjugate of claim 15, wherein the hexose moiety comprises a cluster containing at least three

hexose residues, connected in a branched configuration, and wherein the cluster is conjugated via a single point of attachment to the annexin.

5 17. The conjugate of claim 16, wherein the hexose residues are independently selected from the group consisting of galactose, mannose, mannose 6-phosphate, N-acetylglucosamine, pentamannosyl phosphate, glucose, N-galactosamine, N-acetylgalactosamine, thioglycosides of galactose, D-galactosides and glucosides.

10 18. The conjugate of claim 17, wherein the hexose residue is N-acetylgalactosamine.

15 19. The conjugate of claim 15 or 18, wherein the annexin is annexin V.

20 20. The conjugate of claim 19, wherein the amino acid at position 316 of the annexin is mutated to serine.

20 21. The conjugate of claim 19, wherein the modification of the annexin comprises an amino acid extension at the N-terminus, the amino acid extension comprising the accessible sulfhydryl group.

25 22. The conjugate of claim 21, wherein the extension comprises at least about ten amino acids.

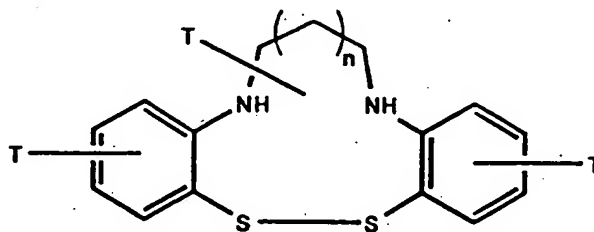
23. The conjugate of claim 21, wherein the extension comprises at least about six amino acids.

24. The conjugate of claim 15, wherein the accessible sulfhydryl group is provided by cysteine.

25. The conjugate of claim 21, wherein the accessible sulfhydryl group is provided by cysteine.

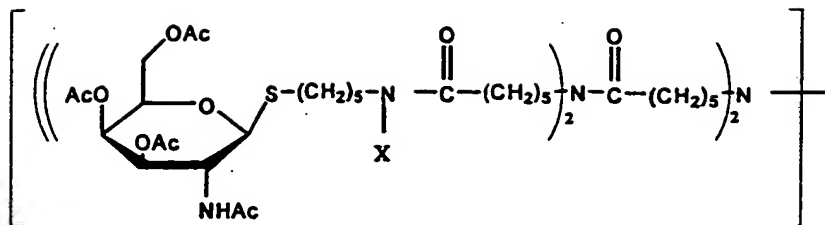
26. The conjugate of claim 15 or 25, wherein the N_xS_y chelating compound comprises an N_2S_2 chelating compound.

27. The conjugate of claim 26, wherein the chelating compound has the following structure:



wherein T is H, CH_3 , or bears a functional group and n is 0 or 1.

28. The conjugate of claim 16 or 27, wherein the cluster comprises:



wherein X is H or CH₃.

29. The conjugate of claim 28, wherein the conjugate has the following configuration:

cluster-modified annexin V-chelating compound.

30. The conjugate of claim 28, wherein the conjugate has the following configuration:

chelating compound-cluster-modified annexin V.

31. The conjugate of claim 28, wherein the conjugate further comprises a cleavable linker between the chelating compound and cluster.

32. The conjugate of claim 31, wherein the cleavable linker is selected from the group consisting of monosaccharides, polysaccharides, polyamino acids, hydroxyalkyl acrylamides, polyethylene glycol based hydrophilic polymers, biodegradable polymers containing an ether or ester linkage, dextran or hemisuccinyl

esters.

33. The conjugate of claim 32, wherein the conjugate has the following configuration:

5 chelating comound-cleavable linker-cluster-modified
annexin V.

34. The conjugate of any one of claims 15, 28 and
32, further comprising a radionuclide complexed by the
10 chelating compound, wherein the radionuclide is selected
from the group consisting essentially of F-18, Cu-64, Ga-
67, Ga-68, Re-186, Re-188, I-123, I-125, Cu-67, Tc-99m,
Tc-94, Ru-95 and In-111.

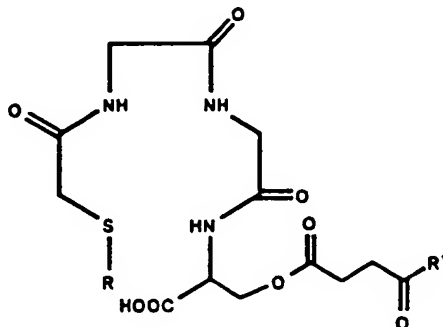
15 35. The conjugate of claim 34, wherein the
radionuclide is technetium-99m.

36. A conjugate comprising:
 an annexin; and
20 an esterase-sensitive N_xS_y chelating compound
conjugated to the annexin.

37. The conjugate of claim 36, wherein the annexin
is annexin V.

25 38. The conjugate of claim 37, wherein the N_xS_y
chelating compound is the N_3S chelating compound.

39. The conjugate of claim 38, wherein the N_3S chelating compound is of the following formula:



wherein R is ethoxyethyl and R^1 is tetrafluorophenyl.

5

40. The conjugate of claim 36 or 39, further comprising a diagnostic radionuclide complexed by the chelating compound.

10

41. The conjugate of claim 40, wherein the radionuclide is selected from the group consisting essentially of F-18, Cu-64, Ga-67, Ga-68, Re-186, Re-188, I-123, I-125, Cu-67, Tc-99m, Tc-94, Ru-95 and In-111.

15

42. The conjugate of claim 41, wherein the radionuclide is technetium-99m.

43. The conjugate of claim 36, wherein the conjugate further comprises a hexose moiety recognized by a

mammalian liver receptor, and wherein the hexose moiety is conjugated to the annexin directly or via the chelating compound and the chelating compound is conjugated to the annexin directly or via the hexose moiety.

5

44. A conjugate comprising:

an annexin multimer;

a hexose moiety recognized by a mammalian liver receptor; and

10

a N_xS_y chelating compound, wherein the hexose moiety is conjugated to the multimer directly or via the chelating compound and the chelating compound is conjugated to the multimer directly or via the hexose moiety.

15

45. The conjugate of claim 44, wherein the hexose moiety comprises a cluster containing at least three hexose residues, connected in a branched configuration, and wherein the cluster is conjugated at a single point of attachment to the multimer.

20

46. The conjugate of claim 45, wherein the hexose residues are independently selected from the group consisting of galactose, mannose, mannose 6-phosphate, N-acetylglucosamine, pentamannosyl phosphate, glucose, N-galactosamine, N-acetylgalactosamine, thioglycosides of galactose, D-galactosides and glucosides.

25

47. The conjugate of claim 46, wherein the hexose residue is N-acetylgalactosamine.

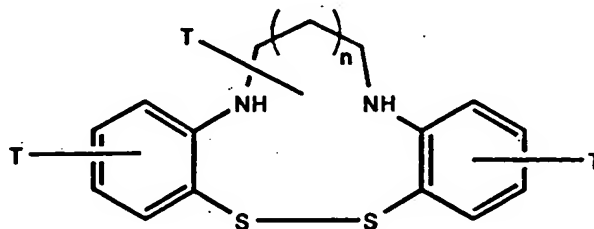
48. The conjugate of claim 44 or 47, wherein the annexin is annexin V.

49. The multimer of claim 44, wherein the multimer comprises two or more modified annexin molecules which are linked by disulfide bonds between one or more of the accessible sulfhydryl groups on the respective annexins.

50. The multimer of claim 44, wherein the multimer is a dimer.

51. The conjugate of claim 44 or 48, wherein the N_xS_y chelating compound is an N_2S_2 chelating compound.

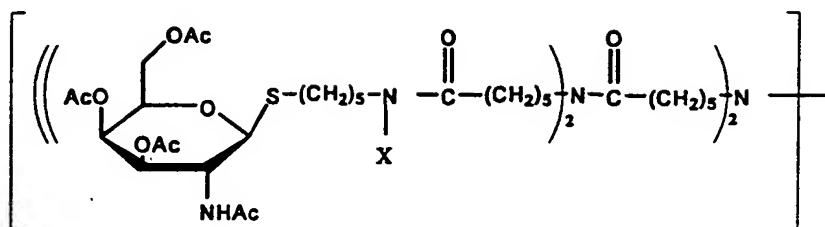
52. The conjugate of claim 51, wherein the N_2S_2 chelating compound is of the following formula:



and wherein T is H, CH_3 , or bears a functional group and n

is 0 or 1.

53. The conjugate of claim 52, wherein the cluster comprises:



wherein X is H or CH₃.

54. The conjugate of claim 53, wherein the conjugate has the following configuration:
10 cluster-multimer-chelating compound.

55. The conjugate of claim 53, wherein the conjugate has the following configuration:
15 chelating compound-cluster-multimer.

56. The conjugate of claim 53, wherein the conjugate further comprises a linker between the chelating compound and cluster.
20

57. The conjugate of claim 56, wherein the cleavable linker is selected from the group consisting of

monosaccharides, polysaccharides, polyamino acids, hydroxyakyl acrylamides, polyethylene glycol based hydrophilic polymers, biodegradable polymers containing an ether or ester linkage, dextran or hemisuccinyl esters.

5

58. The conjugate of claim 57, wherein the conjugate has the following configuration:

chelating compound-cleavable linker-multimer.

10

59. The conjugate of claim 44 or 53, wherein the conjugate further comprises a diagnostic radionuclide complexed by the chelating compound.

15

60. The conjugate of claim 59, wherein the radionuclide is selected from the group consisting essentially of F-18, Cu-64, Ga-67, Ga-68, Re-186, Re-188, I-123, I-125, Cu-67, Tc-99m, Tc-94, Ru-95, and In-111.

20

61. The conjugate of claim 60, wherein the radionuclide is technetium-99m.

25

62. A conjugate comprising:

a modified annexin, wherein the modification provides an acessible sulfhydryl group; and

a N_xS_y chelating compound conjugated to the annexin.

63. A conjugate comprising:

a modified annexin, wherein the modification provides an accessible sulfhydryl group; and
an esterase-sensitive N_xS_y chelating compound conjugated to the annexin.

5 64. A conjugate comprising:
 an annexin multimer; and
 a N_xS_y chelating compound conjugated to the annexin.

10 65. A conjugate comprising:
 an annexin multimer; and
 an esterase-sensitive N_xS_y chelating compound
 conjugated to the annexin.